MACROLIDE FOR ASTHMA CONTROL

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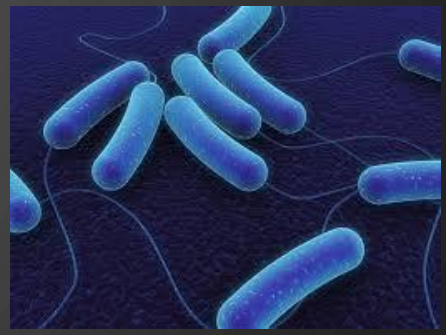
QUESTION

- 평소 천식으로 High dose ICS-LABA, montelukast, low dose theophylline을 사용 중인 환자가 잦은 급성 악화로 내원하였고 반복적으로 경구 prednisolone을 처방하였습니다. 이 환자에게 조절제로서 macrolide를 추가하는 것이 도움이 될 수 있다고 생각하십니까?

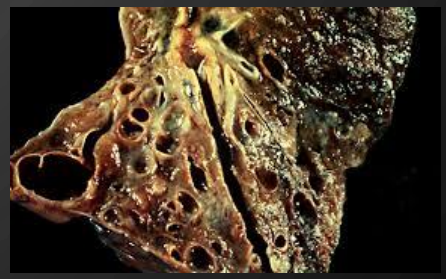
YES / NO

MACROLIDE

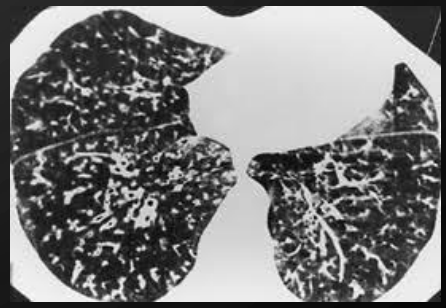
1. ANTIMICROBIAL



2. IMMUNOMODULATION



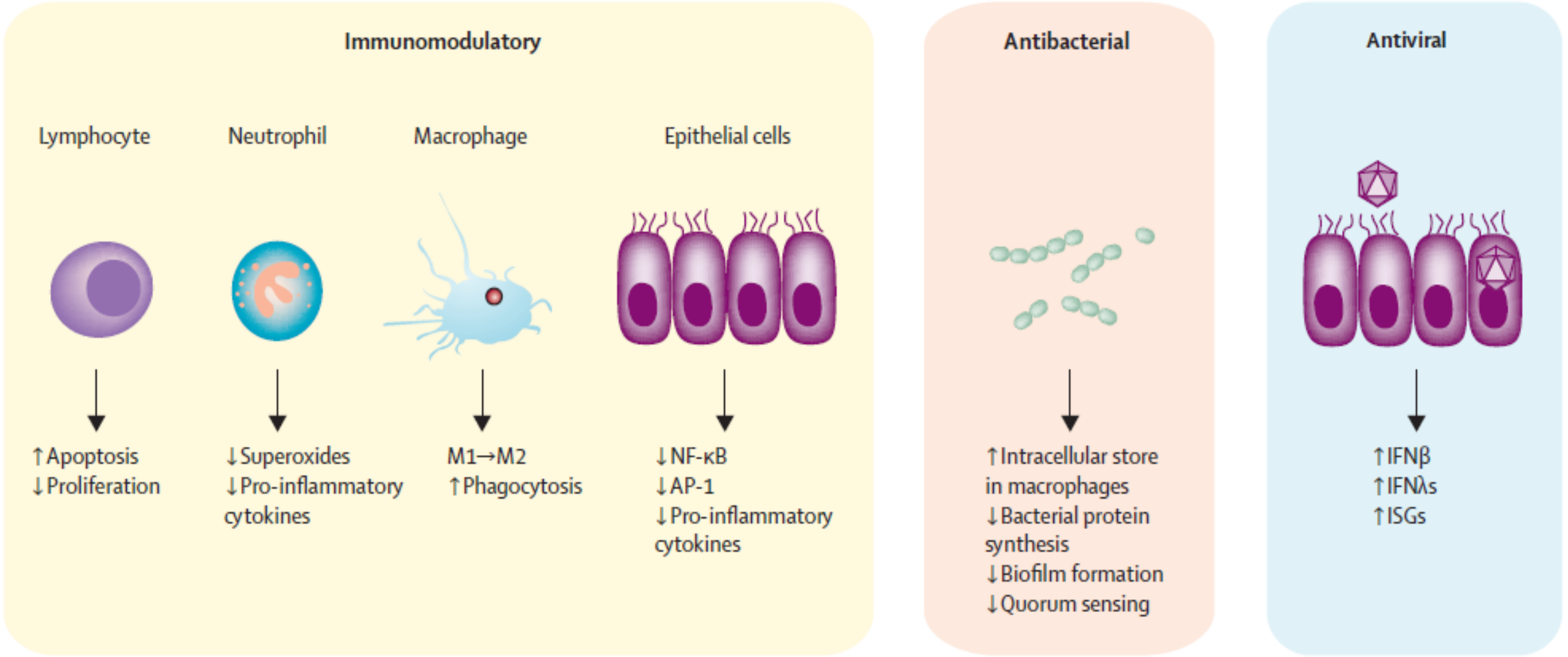
3. ANTIVIRAL POTENTIAL



IMMUNOMODULATION RATHER THAN ANTIBIOTICS

- Up to 3 months to show significant effect
- Doses lower than MIC are effective
- Also effective in patients with macrolide-resistant pathogen
- Bacteria in post-treatment sputum
- Only seen in 14- or 15-membered macrolides (erythro-, clarithro-, roxithro-, azithromycin)

Clin Microbiol Rev 2010;23(3):590-615



Lancet Respir Med 2014;2:657-670

MACROLIDES FOR ASTHMA

Macrolides have Immunomodulatory effect

Asthma is an inflammatory disease

Infection is an important cause of asthma attack

CLINICAL TRIALS

Study	N	Macrolide	Duration	Benefit	Comment
Cameron 2013	71	Azithromycin	12 weeks	No	Smoker asthmatics
Brusselle 2013	109	Azithromycin	26 weeks	Some	Non-eosinophilic subgroup / AQLQ
Hahn 2012	75	Azithromycin	11 weeks	Some	In open-label group / AQL
Sutherland 2010	92	Clarithromycin	16 weeks	Some	Only for PC20
Simpson 2008	45	Clarithromycin	8 weeks	Some	Non-eosinophilic subgroup / AQLQ / IL-8
Hahn 2006	45	Azithromycin	5 weeks	Some	For overall symptom score
Kostadima 2004	63	Clarithromycin	8 weeks	Some	For PC20
Kraft 2002	52	Clarithromycin	6 weeks	Some	For FEV1 and cytokines
Black 2001	219	Roxithromycin	6 weeks	Some	Evening PEF
Amayasu 2000	17	Clarithromycin	8 weeks	Some	PC20, symptoms, sputum eosinophil
Shoji 1999	14	Roxithromycin	8 weeks	Some	Symptom score, blood/sputum eosinophil

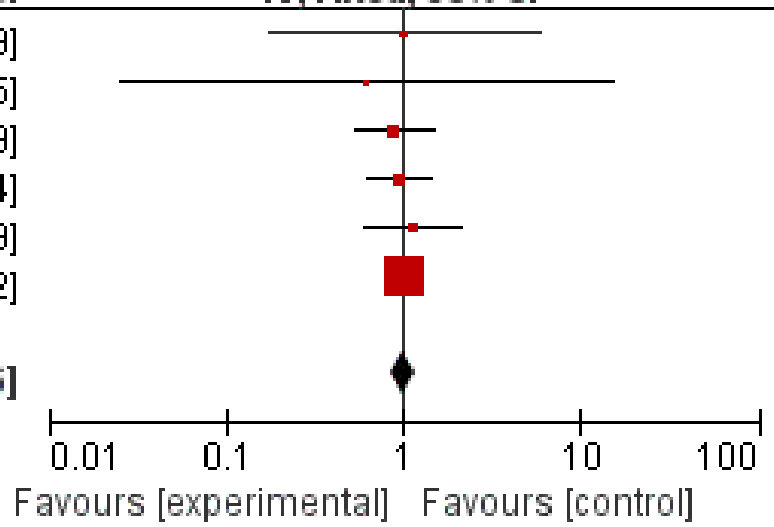
SYSTEMATIC REVIEWS AND META-ANALYSES

Meta-analyses	Period	No. of Studies	Patient	Results
Cochrane 2008	~ May 2007	7	Children / Adult	Benefit for Sx Insufficient studies
Mikailov A, 2013	~ Dec 2009	6	Children	Benefit for Steroid-sparing Insufficient studies
Reiter J, 2013	~ Jan 2013	12	Children / Adult	Benefit for PEF (adult) Benefit for Sx (heterogenous) Benefit for QOL Benefit for AHR Overall, insufficient studies

SR AND META-ANALYSIS

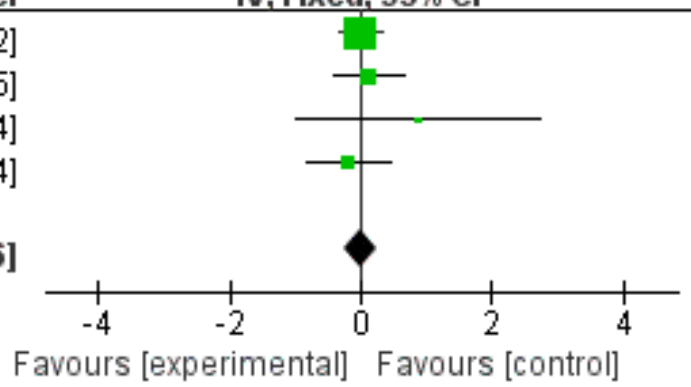
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Amayasu 2000	0.01	0.9	0.8%	1.01 [0.17, 5.89]
Brusselle 2013	-0.47	1.63	0.3%	0.63 [0.03, 15.25]
Kostadima 2004	-0.12	0.265	9.6%	0.89 [0.53, 1.49]
Kraft 2002	-0.05	0.21	15.3%	0.95 [0.63, 1.44]
Shoji 1999	0.12	0.3137	6.8%	1.13 [0.61, 2.09]
Sutherland 2010	0	0.1	67.3%	1.00 [0.82, 1.22]
Total (95% CI)			**100.0%**	**0.99 [0.84, 1.16]**

Heterogeneity: Chi² = 0.47, df = 5 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

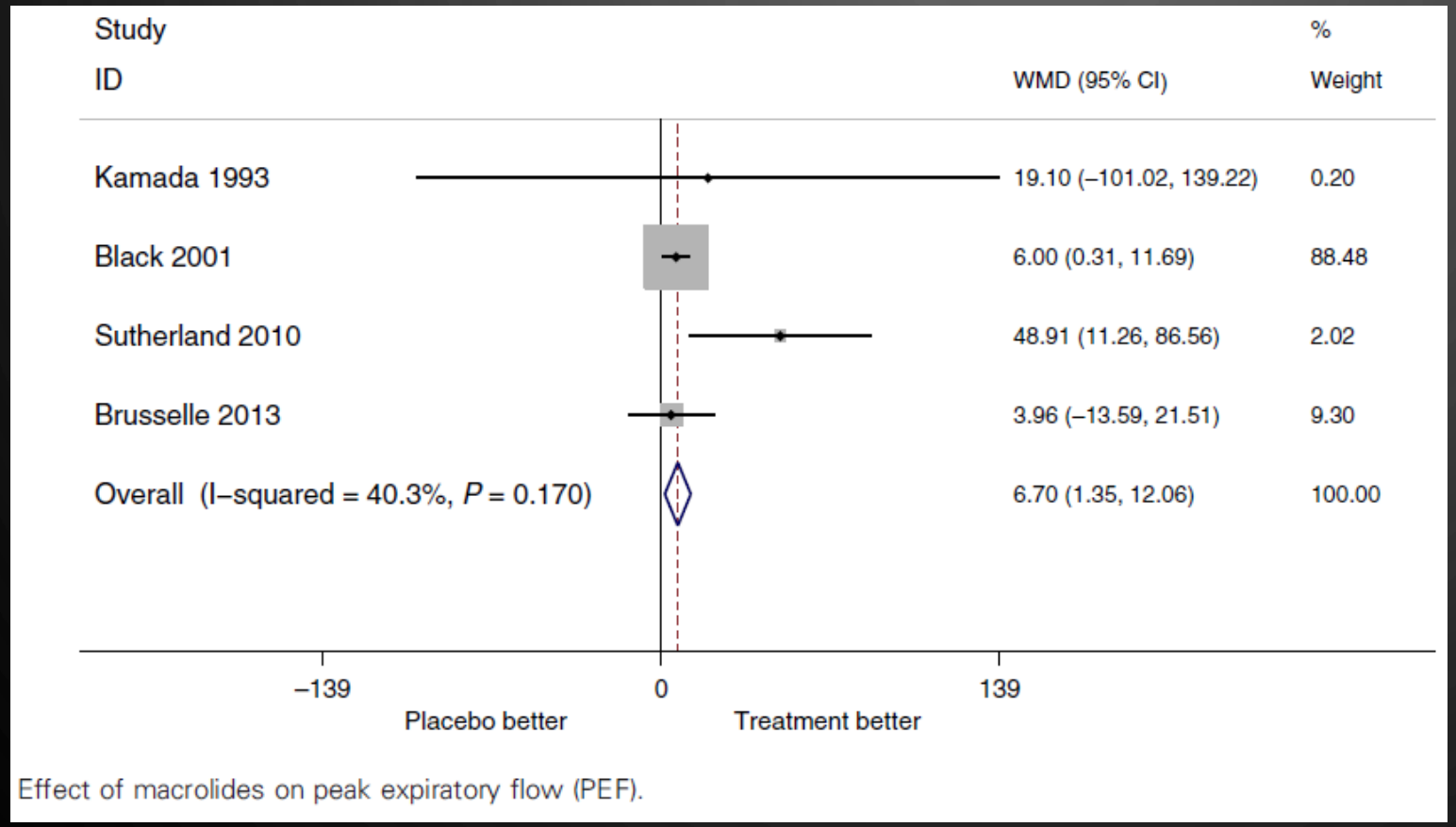


Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Brusselle 2013	-0.05	0.98	55	-0.04	0.76	54	60.3%	-0.01 [-0.34, 0.32]
Hahn 2012	-0.34	0.88	29	-0.45	1	20	22.1%	0.11 [-0.43, 0.65]
Kapoor 2010	2.68	3.17	20	1.8	2.83	20	1.9%	0.88 [-0.98, 2.74]
Simpson 2008	-0.3	0.92	23	-0.1	1.28	23	15.7%	-0.20 [-0.84, 0.44]
Total (95% CI)			**127**			**117**	**100.0%**	**0.00 [-0.25, 0.26]**

Heterogeneity: Chi² = 1.39, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)



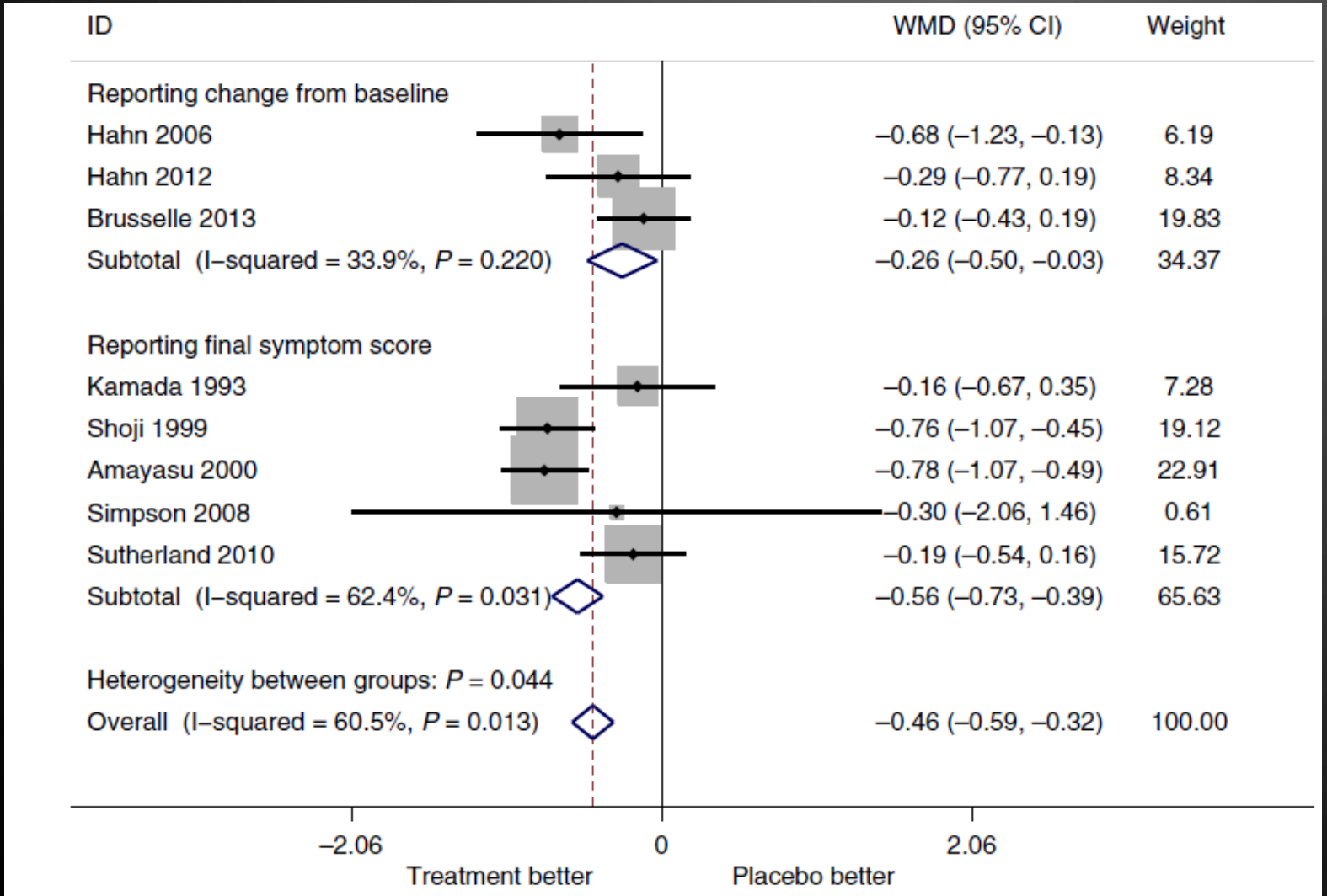
SR AND META-ANALYSIS



Effect of macrolides on peak expiratory flow (PEF).

Reiter J, et al. Allergy 2013;68:1040-1049

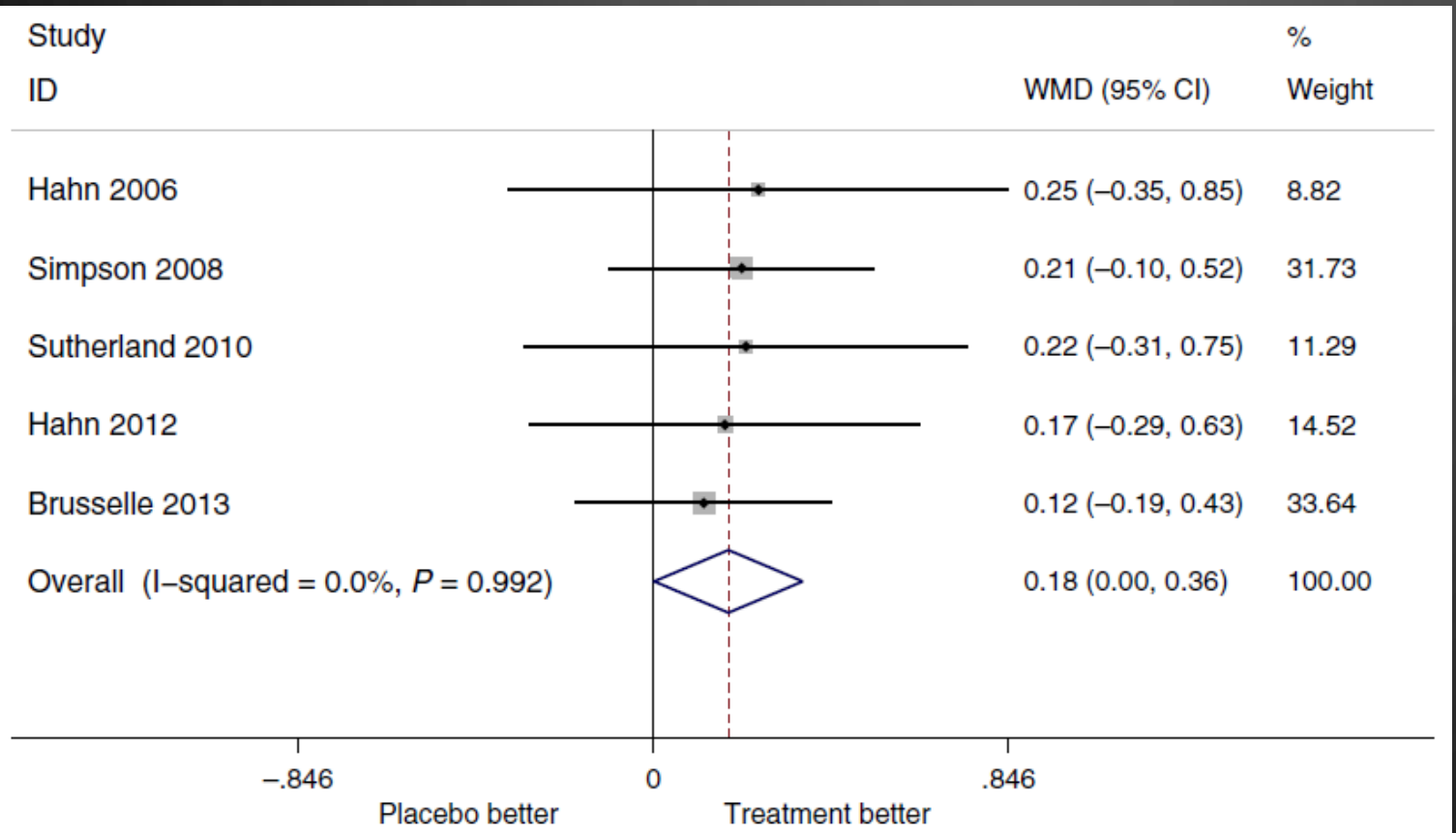
SR AND META-ANALYSIS



Effect of macrolides on symptom scores.

Reiter J, et al. Allergy 2013;68:1040-1049

SR AND META-ANALYSIS



Effect of macrolides on quality-of-life (QOL) score.

Reiter J, et al. Allergy 2013;68:1040-1049

UNTIL NOW, SR AND META-ANALYSES SUGGEST

Lung Function	**NO EVIDENCE**
Attack ACQ	**NO EVIDENCE**
Sx QOL	**POSSIBLE SOME BENEFIT**

THE 'AZISAST' TRIAL

Study Population	109 Adult asthma patient (55 vs 54), never or ex-smokers
Severity	GINA step 4~5, > 2 exacerbations within year
Base Medications	High dose ICS-LABA
Intervention	Azithromycin 250mg three times / week for 26 weeks
Primary endpoint	Severe exacerbation or LRTI
Secondary endpoint	FEV1, PEF, AQLQ, ACQ

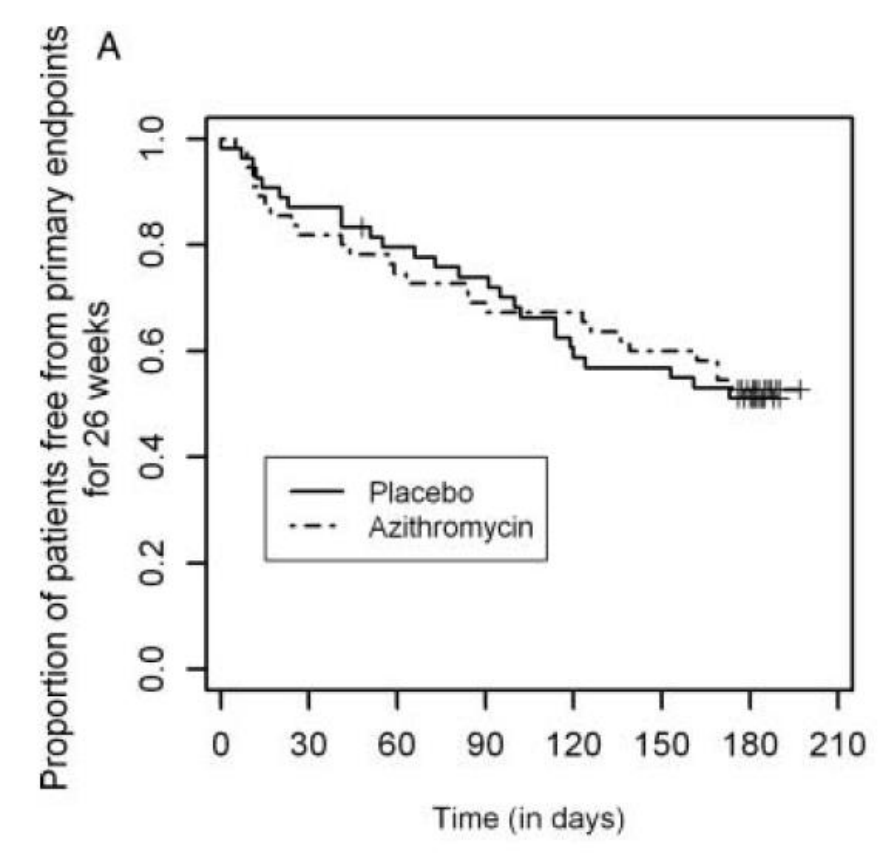
Brusselle GG, et al. Thorax 2013;68:322-329

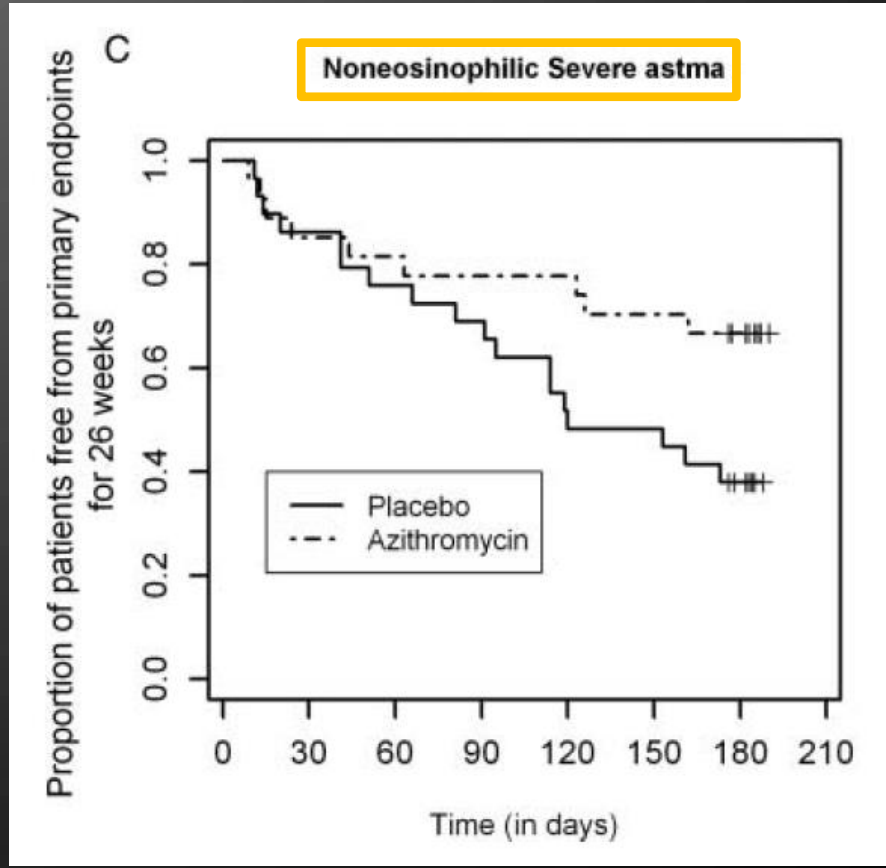
THE 'AZISAST' TRIAL

Outcome	At 26 weeks after randomisation			
	Placebo (N=45–50)Mean (SD)	Azithromycin (N=47–53)Mean (SD)	DifferenceMean (95% CI)	p Value
Change in ACQ score, baseline to week 10 or 26	−0.12 (0.70)	−0.24 (0.93)	−0.12 (−0.44 to 0.21)	0.485
Change in AQLQ total score, baseline to week 10 or 26	0.20 (0.73)	0.32 (0.89)	0.12 (−0.20 to 0.44)	0.467
Absolute change in morning PEF, baseline to week 10 or 26 (l/min)	−5.77 (48.20)	−1.81 (45.27)	3.96 (−15.40 to 23.32)	0.686
Absolute change in evening PEF, baseline to week 10 or 26 (l/min)	−4.65 (78.68)	−0.81 (48.47)	3.84 (−23.10 to 30.78)	0.778
Change in pre-BD FEV_1, baseline to week 10 or 26 (%)	−0.90 (11.79)	−0.02 (10.06)	0.88 (−3.44 to 5.19)	0.688
Change in post-BD FEV_1, baseline to week 10 or 26 (%)	−0.66 (8.84)	1.29 (12.50)	1.95 (−2.42 to 6.33)	0.378
Change in use of rescue medication (number of puffs per day)	0.24 (2.11)	0.08 (1.14)	−0.16 (−0.88 to 0.55)	0.655
Change in FeNO (ppb), median (Q1; Q3)	2.1 (−4.2; 6.0)	0.5 (−6.7; 6.7)	−1.6	0.666

Brusselle GG, et al. Thorax 2013;68:322-329

THE ‘AZISAST’ TRIAL





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Simpson JL, et al. 2008

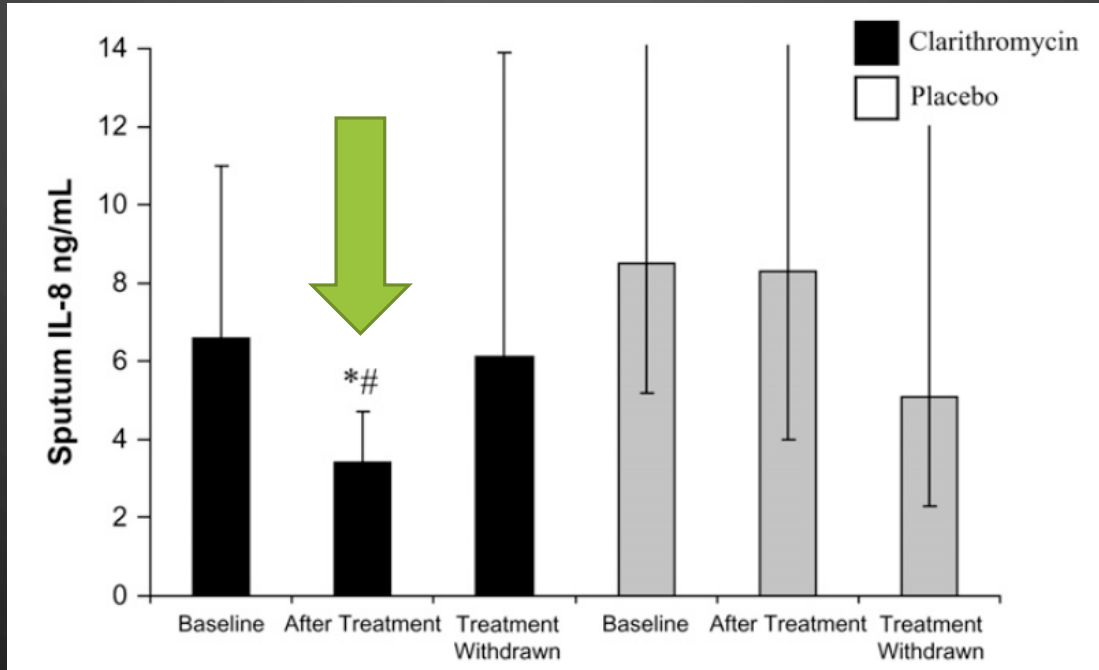


Figure 3. Sputum IL-8 concentrations before treatment, after 8 weeks' treatment with clarithromycin and placebo, and after treatment withdrawal in participants with noneosinophilic asthma. $^{*}P = 0.0046$ versus before treatment; $^{\#}P = 0.0096$ after treatment was withdrawn.

Am J Respir Crit Care Med 2008;177:148-155

Simpson JL, et al. 2008

TABLE 4. INFLAMMATORY PARAMETERS AND ASTHMA QUALITY-OF-LIFE TOTAL SCORE BEFORE AND AFTER TREATMENT FOR PARTICIPANTS WITH NONEOSINOPHILIC ASTHMA

	Clarithromycin			Placebo		
	Before	After	*P**	Before	After	*P**
IL-8 protein, ng/ml	6.6 (2.1–11.0)	3.4 (1.9–4.7)†	0.0046	8.5 (5.2–28.9)	8.3 (4.0–31.4)	0.917
IL-8 gene expression	40.2 (8.9–69.9)	14.3 (3.6–22.5)	0.0229	12.6 (7.7–104.3)	15 (3.1–142)	0.790
Neutrophils × 10^4/ml	110.7 (32.8–496.8)	70.7 (23.6–131)	0.0843	254.5 (60.9–503.8)	107.7 (70.1–281.2)	0.2132
Neutrophil elastase, ng/ml	698.4 (150.5–1,637)	491 (174.6–729.9)†	0.0597	1,202 (545–5,880)	1,032 (551.3–7,088)	0.463
Total MMP-9, ng/ml	9,111 (2,280–11,772)	3,183 (1,806–5,115)†	0.0166	6,455 (3,459–14,871)	9,826 (3,415–15,844)	0.959
Total AQLQ score, median (IQR)	5.5 (4.7–6.3)	6.2 (5.6–6.6)	0.0202	6.0 (5.0–6.6)	6.1 (4.8–6.8)	0.900

Am J Respir Crit Care Med 2008;177:148-155

QUESTION

ARDS나 SEPTIC SHOCK 환자에서 CORTICOSTEROID가

도움이 된다 / 도움이 되지 않는다

HETEROGENEITY

LONG-TERM USE AND SAFETY

The NEW ENGLAND JOURNAL of MEDICINE

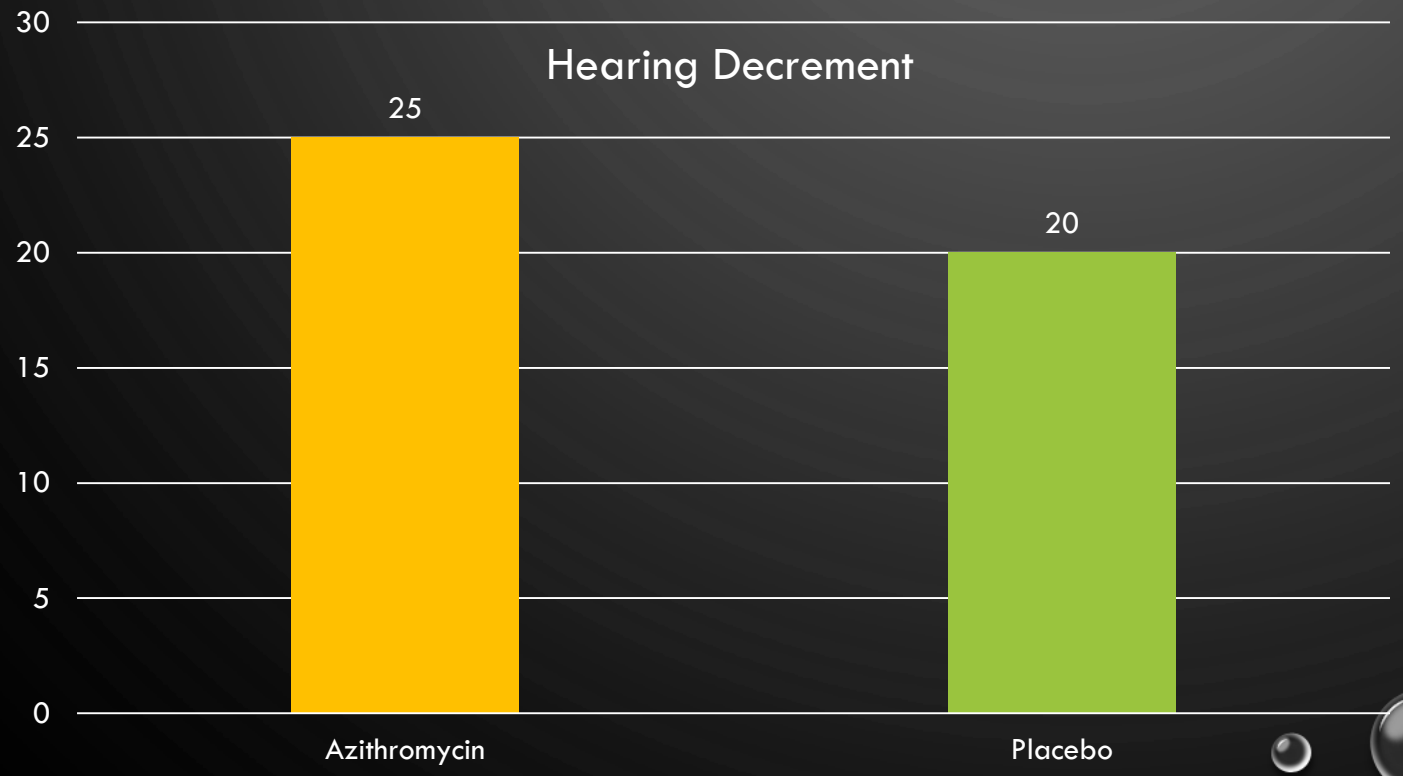
ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., MeiLan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porsasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network

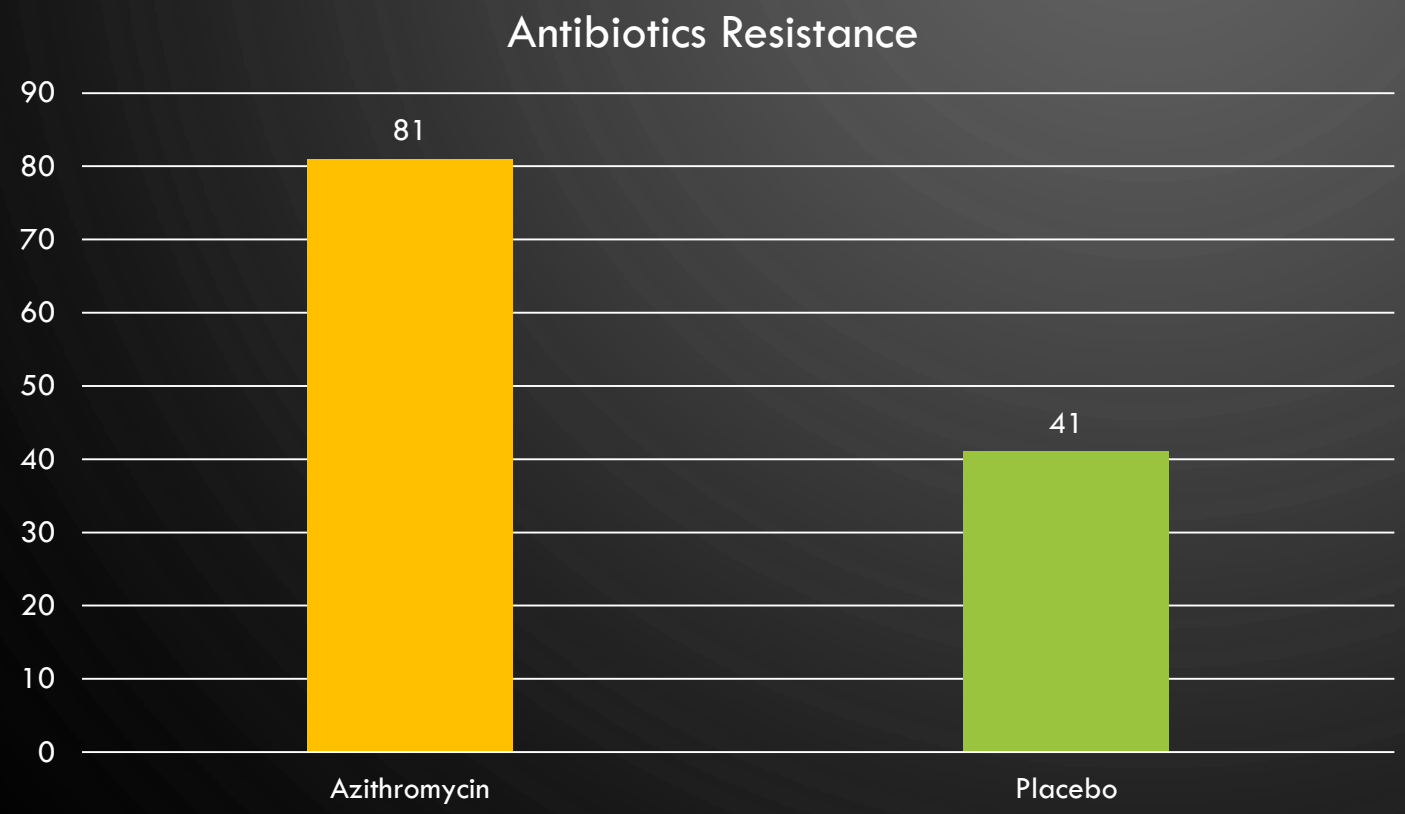
LONG-TERM USE AND SAFETY

- 1142 Patients
- Azithromycin 250mg qd vs placebo for 'A YEAR'



N Engl J Med 2011;365:689-698

LONG-TERM USE AND SAFETY



N Engl J Med 2011;365:689-698

SUMMARY

MACROLIDES FOR ASTHMA CONTROL

1. Theoretically reasonable
2. Benefit for Symptom Control and Quality of Life
3. Possible Benefit for Certain Group of Asthma Patients
4. Acceptable Safety Profile
5. Why Not?

QUESTION

- 평소 천식으로 High dose ICS-LABA, montelukast, low dose theophylline을 사용 중인 환자가 잦은 급성 악화로 내원하였고 반복적으로 경구 prednisolone을 처방하였습니다. 이 환자에게 조절제로서 macrolide를 추가하는 것이 도움이 될 수 있다고 생각하십니까?

YES / NO